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**PRE-APPEAL BRIEF REQUEST FOR REVIEW**

Docket Number (Optional)

1821.0070004/EJH/T-M

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Application Number

09/987,456

Filed

November 14, 2001

First Named Inventor

Maurice ZAUDERER

Art Unit

1639

Examiner

Epperson, J.D.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).

Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.☐ assignee of record of the entire interest.  
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.  
(Form PTO/SB/96)☐ attorney or agent of record.  
Registration number \_\_\_\_\_☒ attorney or agent acting under 37 CFR 1.34.Registration number if acting under 37 CFR 1.34 55,472  
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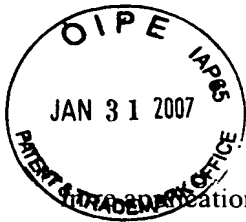
  
Date  
January 31, 2007

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below\*.

☐ \*Total of \_\_\_\_\_ forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: ZAUDERER *et al.*

Appl. No.: 09/987,456

Filed: November 14, 2001

For: ***In Vitro Methods of Producing and  
Identifying Immunoglobulin Molecules in  
Eukaryotic Cells***

Confirmation No.: 6770

Examiner: Epperson, Jon D.

Atty. Docket: 1821.0070004/EJH/T-M

**Arguments to Accompany the Pre-Appeal Brief Request for Review**

***Mail Stop AF***

Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450

***Summary of Request***

The Examiner's rejection of claims 84, 88-97, 99, 103, 107-122, and 127-131 under 35 U.S.C. § 103(a) as being unpatentable over Rowlands *et al.*, (WO 93/01296), Zauderer (WO 00/28016), and Waterhouse *et al.* (*Nuc. Acids Res.* 21: 2265-66 (1993)) is improper. Specifically, the Examiner erred by mischaracterizing and disregarding the Declaration of Dr. Walter Storkus and by substituting his own opinion for that of an expert--without presenting any countervailing evidence--in concluding that one of skill in the art would have had a reasonable expectation of success in combining the cited references. Thus, Applicants respectfully request that the obviousness rejection be withdrawn and the claims allowed.

***Argument***

The Examiner maintained the improper rejection over the combination of Rowlands, Zauderer, and Waterhouse in the Office Action of October 31, 2006 ("10/31/06 OA"). Rowlands discloses the expression of a *single* heavy chain and a *single* light chain of a pre-selected antibody (*i.e.*, humanized Campath 1 antibody) in vaccinia virus vectors. Zauderer discloses introduction of *one* vaccinia virus expression library for screening tumor antigens. Waterhouse discloses the expression of heavy and light chain *fragments* in a combinatorial *phage display* library in *prokaryotic cells*. One of ordinary skill in the art would not have been motivated to combine these three references with a reasonable expectation of success.

The present invention is directed to a method of selecting polynucleotides that encode an antigen-specific human immunoglobulin molecule by expressing separate vaccinia virus libraries of immunoglobulin heavy and light chains in mammalian host cells. The Examiner asserted that one of skill in the art would have been motivated to use Zauderer's method of making a single library to make two libraries as in Waterhouse, and to express antibody heavy and light chains as in Rowlands. According to the Examiner, there would have been a reasonable expectation of success because both Zauderer and Rowlands discuss the use of vaccinia virus vectors in mammalian cells and Waterhouse discloses examples of associated heavy and light chains that can be used for screening and/or antibody maturation. 10/31/06 OA at pages 3 and 9-10.

The question at issue is whether one of skill in the art would have been motivated to combine Rowlands with Zauderer and Waterhouse, *with a reasonable expectation of success*, to arrive at the claimed invention. To address this question, Applicants submitted the Declaration of Dr. Walter Storkus with their reply of July 21, 2005. Dr. Storkus is an expert in immunology and was a member of the Scientific Advisory Board (SAB) of Vaccinex, Inc.<sup>1</sup>, at the time the present application was filed. *See* Storkus Declaration and Exhibit A1 thereto. As an SAB member, Dr. Storkus evaluated the claimed technology contemporaneous with the filing of the present application and, therefore, was able to provide an account of his thoughts about the invention *at that time*. Dr. Storkus opined that, at the time, he did not think there was a reasonable expectation of success and he provided specific reasons why he considered phage display methods, such as those disclosed in Waterhouse, to be of limited instructive value for a eukaryotic immunoglobulin screening method. *Id.* at ¶¶ 7-9. Because of the different ways in which prokaryotic and eukaryotic expression systems work and the complexity of getting randomly expressed immunoglobulin heavy and light chains from two different libraries to

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<sup>1</sup> Vaccinex, Inc., is the exclusive licensee of the present invention.

associate, Dr. Storkus stated that, even in view of the cited references, at the time the present application was filed, he would not have expected to achieve success with the claimed invention.

*Id.* Nevertheless, the Examiner disregarded the opinion of Dr. Storkus in favor of the Examiner's own opinion of how one of skill in the art would regard Rowlands, Zauderer, and Waterhouse, and phage display methods in general.

The Examiner erred both factually and legally by disregarding the Storkus Declaration and maintaining the rejection. The Examiner erred factually by contending that the Storkus Declaration is "ambiguous," and that Dr. Storkus did not specify the time at which the idea for the present invention was first presented to him. *See* 10/31/06 OA at page 30. It is clear from his Declaration that the idea was presented to Dr. Storkus in his capacity as an SAB member of Vaccinex, Inc., and that he was an SAB member at the time the present application was filed (*i.e.*, from 2001 to 2004). *See* Storkus Declaration at pages 1-2. Therefore, the Examiner erred by asserting that "[w]e don't know what Dr. Storkus would have stated 'at the filing date of the application' as required," and that the Storkus Declaration "provide[s] no evidentiary support for Applicants." *See* 10/31/06 OA at pages 30-31.

The Examiner erred legally by substituting his opinion for that of an expert. *See In re Zeidler*, 682 F.2d 961, 966-67 (C.C.P.A. 1982) (holding that the decision of the Board of Patent Appeals and Interferences constituted reversible error, "the board having erroneously substituted its judgment for that of an established expert in the art."). For example, the Examiner has continued to rely on Waterhouse to show "that the production of two libraries ... will lead to more favorable antibodies via a co-selection process, regardless of how those antibodies are produced," 10/31/06 OA at page 30 (emphasis in original), and has asserted that "the prokaryotic/eukaryotic distinctions to which Applicants refer ... are not at issue in this case." Office Action of April 21, 2006, at page 28. However, as indicated in the Storkus Declaration,

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these differences are at the *very heart* of why one of skill in the art would not have had a reasonable expectation of success in combining Waterhouse with Rowlands and Zauderer. *See* Storkus Declaration at ¶¶ 7-9. In particular, Dr. Storkus stated: 1) that he thought that it would not be practical to screen the number of eukaryotic cells necessary to find antigen-specific antibodies, as was possible via screening phage; and 2) because of the differences in the conditions of eukaryotic cytoplasm as compared to prokaryotic periplasm, he thought that random pairs of immunoglobulin heavy and light chains would fail to associate properly in eukaryotic cells and therefore would not allow selection of antigen-specific antibodies. *Id.* at ¶ 7. Dr. Storkus further stated that expressing a single antibody, as in Rowlands, is "far simpler" than expressing heavy and light chain pairs from separate libraries, because the Rowlands antibody had already been selected for heavy and light chains that paired correctly and efficiently to specifically bind antigen. *Id.* at ¶ 9. Dr. Storkus also explicitly stated that Zauderer does not address the concern of assembling heavy and light chains from two separate libraries in eukaryotic cells because only one library was introduced into host cells. *Id.* Therefore, Dr. Storkus concluded that his expectations would not have changed in view of these references. *Id.*

The Examiner has provided no specific evidence or relevant scientific rationale to counter the statements of Dr. Storkus or support the erroneous assumption that, simply because two libraries had been used for phage display in prokaryotic cells, one of skill in the art would expect the claimed two library screening/expression system to be successful in eukaryotic cells. Indeed, the only "evidence" cited by the Examiner are passages from Rowlands, Zauderer, and Waterhouse, and a few paragraphs from Applicants' own specification that mention phage display methods (and, more specifically, the shortcomings of phage display methods). *See* 10/31/06 OA at pages 22-23 and 29. Dr. Storkus gave explicit reasons why he did not think there was a reasonable expectation of success, even in view of Rowlands, Zauderer, and Waterhouse.

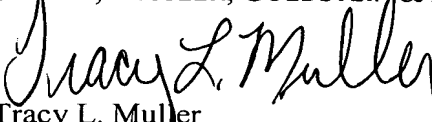
Hence, citing excerpts from these references does not lend support to the Examiner's position. Likewise, the cited paragraphs from Applicants' own specification do not support the Examiner's position because Applicants do not dispute the fact that combinatorial libraries for selecting immunoglobulins have been generated in phage. Rather, the relevant inquiry is whether one of skill in the art would have had been motivated to combine Rowlands, Zauderer, and a phage display reference like Waterhouse to arrive at the claimed invention *with a reasonable expectation of success*. Dr. Storkus explained why, in his opinion as an immunology expert who evaluated the claimed technology at the time the present application was filed and based on his knowledge at that time, he did not think there was a reasonable expectation of success. By disregarding Dr. Storkus's explanation without providing any supporting evidence to contrary, the Examiner has improperly substituted his own opinion for that of an expert.

*Summary*

For the reasons set forth above, the Examiner's rejection of the pending claims under 35 U.S.C. § 103(a) is legally and factually flawed, and the Examiner has not established a legally proper *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the obviousness rejection be withdrawn and the claims allowed.

Respectfully submitted,

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